(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 November 2003 (20.11.2003)

PCT

(10) International Publication Number
WO 03/094951 A1

(51) International Patent Classification[7]: A61K 38/28, C07K 14/62

(21) International Application Number: PCT/DK03/00239

(22) International Filing Date: 10 April 2003 (10.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2002 00684 7 May 2002 (07.05.2002) DK

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/094951 A1

(54) Title: SOLUBLE FORMULATIONS COMPRISING INSULIN ASPART AND INSULIN DETEMIR

(57) Abstract: A stable, soluble insulin formulations having both a fast and a long action.

SOLUBLE FORMULATIONS COMPRISING INSULIN ASPART AND INSULIN DETEMIR

Introduction

This invention relates to a pharmaceutical formulation containing insulin aspart and insulin detemir wherein insulin detemir has a profile of action which is identical or substantially identical with the profile of action of insulin detemir in the absence of insulin aspart. Furthermore, this invention relates to the additional aspects mentioned in the claims below.

The main object of this invention is to overcome or ameliorate at lest some of the disadvantages of the prior art. Hence, the more specific objects mentioned below are more or less fulfilled.

Background of this invention

Diabetes is a general term for disorders in man having excessive urine excretion as in diabetes mellitus and diabetes insipidus. Diabetes mellitus is a metabolic disorder in which the ability to utilize glucose is partly or completely lost. About 5% of all people suffer from diabetes. Since the introduction of insulin in the 1920's, continuous strides have been made to improve the treatment of diabetes mellitus. To help avoid extreme glycemia levels, diabetic patients often practice multiple daily injection therapy, whereby, for example, fast-acting insulin is administered with each meal and long-acting or intermediate-acting insulin is administered once or twice daily to cover the basal need.

In the treatment of diabetes mellitus, many varieties of insulin formulations have been suggested and used, such as regular insulin, isophane insulin (designated NPH), insulin zinc suspensions (such as Semilente®, Lente®, and Ultralente®), and biphasic isophane insulin. As diabetic patients are treated with insulin for several decades, there is a major need for safe and life quality improving insulin formulations. Some of the commercial available insulin formulations are characterized by a fast onset of action and other formulations have a relatively slow onset but show a more or less prolonged action. Fast-acting insulin formulations are usually solutions of insulin, while retarded acting insulin formulations can be suspensions containing insulin in crystalline and/or amorphous form precipitated by addition of zinc salts alone or by addition of protamine or by a combination of both. In addition, some patients are using formula-

tions having both a fast onset of action and a more prolonged action. Such a formulation may be an insulin solution wherein protamine insulin crystals are suspended. Some patients do themselves prepare the final formulation by mixing a fast acting insulin solution with a protracted acting insulin suspension formulation in the ratio desired by the patient in question.

Human insulin consists of two polypeptide chains, the so-called A and B chains which contain 21 and 30 amino acid residues, respectively. The A and B chains are interconnected by two cystine disulphide bridges. Insulin from most other species has a similar construction, but may not contain the same amino acid residues at the same positions.

The development of the process known as genetic engineering has made it possible to prepare a great variety of insulin compounds being analogous to human insulin. In these insulin analogues, one or more of the amino acids have been substituted with other amino acids which can be coded for by the nucleotide sequences.

Normally, insulin formulations are administered by subcutaneous injection. What is important for the patient, is the action profile of the insulin formulation which is the action of insulin on the glucose metabolism as a function of the time from the injection. In this profile, inter alia, the time for the onset, the maximum value, and the total duration of action are important. A variety of insulin formulations with different action profiles are desired and requested by the patients. One patient may, on the same day, use insulin formulations with very different action profiles. The action profile requested is, for example, depending on the time of the day and the amount and composition of any meal eaten by the patient.

There is a big need for insulin formulations with different profiles of release of insulin. A patent may, during the day, used insulin formulations with different profiles of release. For example, the patient may, before a meal, use a fast-acting insulin formulation with no retarded action. Other patient may, before a meal, use a formulation having both a fast action and a retarded action. In such a formulation having both a fast action and a retarded action, the ratio between fast action and retarded action may vary considerably. Before a patient goes to sleep, the patient may use a long-acting insulin formulation. Some patients will, before they go to sleep, use a formulation having both a fast action and a retarded action.

One object of the present invention is to furnish insulin formulations having a convenient profile of action.

Another object of the present invention is to furnish soluble insulin formulations having both a fast onset of action and also a retarded action.

Another object of the present invention is to furnish insulin formulations having no or only a minor amount of non-dissolved material.

Another object of the present invention is to furnish insulin formulations containing both a fast and long acting insulin component wherein the two insulin components acts as or acts substantially as they would have acted if they had been the only insulin components present in the formulation.

Another object of the present invention is to furnish insulin formulations having a profile of release which is very predictable, both from time to time an also form patient to patient.

Definitions

A systematic chemical name of insulin aspart and insulin detemir is Asp^{B26} human insulin and $Lys^{B29}(N^{\varepsilon}$-tetradecanoyl) des(B30) human insulin, respectively. Collectively they are herein referred to as the insulin components.

The term "U", when used herein, refers to insulin units. For insulin aspart, one unit equals 6 nmol (about 40 µg) and for insulin detemir, one unit equals 24 nmol (about 160 µg).

The content of zinc is expressed per hexamer insulin as a theoretical value, i.e., as the number of zinc atoms per 6 molecules of monomeric insulin, independent on whether all insulin actually is present as hexameric insulin or not.

Description of this invention

It has, surprisingly been found that aqueous insulin formulations comprising about 15-85 % (on a mole to mole basis) of insulin aspart and the remaining part of insulin activity origination from insulin detemir, gives profiles of release which are convenient for different patient groups. Furthermore, the formulations have no or only a minor content of non-dissolved material. In the formulations of this invention, the two insulin components acts as or acts substantially as they would have acted if they had been the only insulin components present. The formulations of the present invention have a profile of release which is very predictable, both from time to time an also form patient to patient.

The pharmaceutical formulation of this invention may be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the pertinent ingredients as appropriate to give the desired end product.

Thus, according to one procedure, on one hand, insulin aspart and, on the other hand, insulin detemir is dissolved in an amount of water, the total volume of which is somewhat less than the final volume of the formulation to be prepared. An isotonic agent, a preservative, and, optionally, a buffer is added as required and the pH value of the solution is adjusted - if necessary - using an acid, for example, hydrochloric acid, or a base, for example, aqueous sodium hydroxide as needed. Finally, the volume of the solution is adjusted with water to give the desired concentration of the ingredients.

In a preferred embodiment of this invention, the formulation contains an agent rendering the solution isotonic, an antimicrobial preservative, a pH-buffering agent, and a suitable zinc salt.

In a preferred embodiment of this invention, the formulation has a total amount of the insulin in the range from about 10 U/ml to about 1500 U/ml, preferably in the range from about 40 U/ml to about 1000 U/ml, more preferred in the range from about 100 U/ml to about 500 U/ml, for example, 100, 200, 400, or 500 U/ml.

In a preferred embodiment of this invention, the preservative is phenol, *m*-cresol or a mixture of phenol and *m*-cresol. In a further preferred embodiment of this invention, the total concentration of phenol and/or *m*-cresol is in the range from about 20 mM to about 50 mM, preferably in the range from about 30 mM to about 45 mM. The concentration of phenol and/or *m*-cresol is, *inter alia*, depending on the concentration of insulin.

In a preferred embodiment of this invention, the formulation has a content of zinc ions at the disposal of insulin in proportions in the range from about 2.3 to about 4.5 Zn^{2+} per hexamer insulin (corresponding to from about 0.38 to about 0.75 Zn^{2+}/monomer insulin). The zinc salt used for preparing the formulations of this invention may, for example, be zinc chloride, zinc oxide or zinc acetate.

In a preferred embodiment of this invention, the isotonic agent is glycerol, mannitol, sorbitol or a mixture thereof at a concentration in the range from about 100 to 250 mM.

In another preferred embodiment of this invention, the formulation contains halogenide ions, preferably as sodium chloride, in an amount corresponding to from about 1 mM to about 100 mM, preferably from about 5 mM to about 40 mM.

In a preferred embodiment of this invention, the pH buffer is sodium phosphate, TRIS (trometamol), N-glycylglycine or L-arginine. Preferably, the pH buffer is a physiologically acceptable buffer in a concentration in the range from about 3 mM to about 20 mM, preferably from about 5 mM to about 15 mM. In a preferred embodiment of this invention, the formulations of this invention have a pH value is in the range from about 7.0 to about 8.0.

In a preferred embodiment of this invention, the formulation of this invention has a content of non-dissolved material below about 0.1 %, preferably below 0.01 % (weight per weight).

Administration of the formulations of this invention may be via any route known to be effective by the physician of ordinary skill. Parenteral and preferably subcutaneous administration is preferred.

The amount of the formulation of this invention that is administered to treat diabetes depends on a number of factors, among which are included the patient's sex, weight, physical activity, and age, diet of the patient, the underlying causes of the condition or disease to be treated, the route of administration and bioavailability, the persistence of the administered insulin or insulin analogues in the body, the specific formulation used, the potency of the insulin or insulin analogue used, a possible combination with other drugs, the severity of the case of diabetes, and the interval between dosages, if any interval. It is within the skill of the ordinary physician to titrate the dose and frequency of administration of the formulation of this invention to achieve the desired result. It is recommended that the daily dosage of the insulin components used in the formulation according to this invention be determined for each individual patient by those skilled in the art in a similar way as for known insulin compositions.

The mentioning herein of references is no admission that they constitute prior art.

Herein, the word "comprise" is to be interpreted broadly meaning "include", "contain" or "comprehend" (*vide*, for example, EPO guidelines C 4.13).

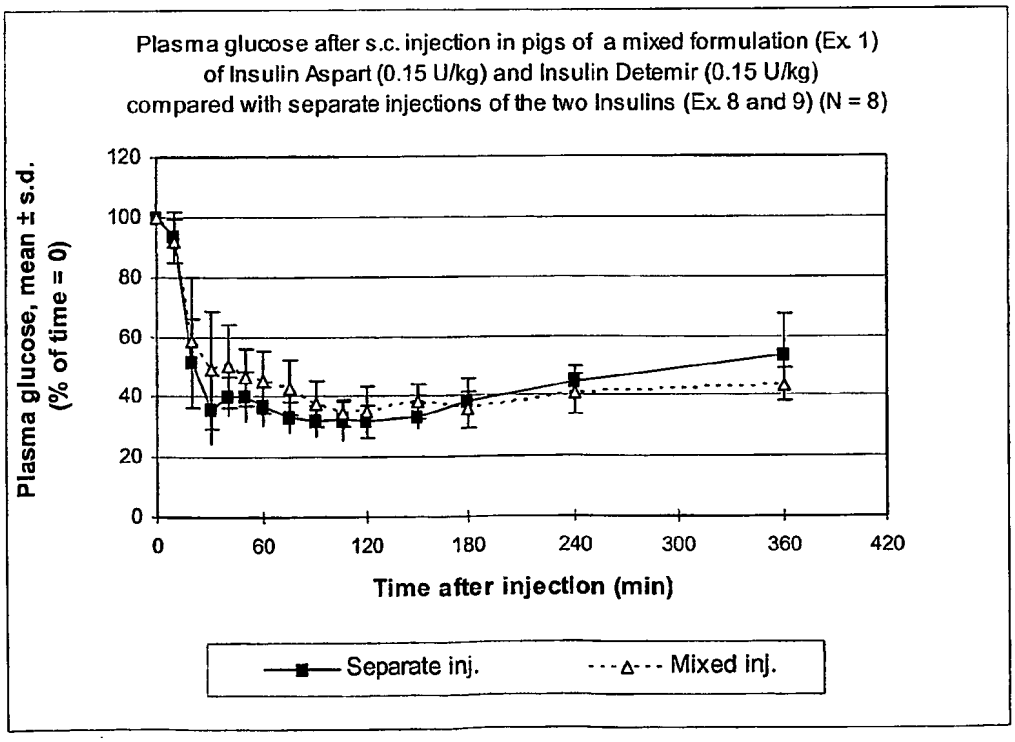
This invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing this invention in diverse forms thereof.

Example 1

67 U insulin per ml containing 50% (U/U) insulin aspart and 50% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 33.3 U/ml (200 nmol/ml), Insulin detemir 33.3 U/ml (800 nmol/ml), phenol 1.50 mg/ml (16 mM), *m*-cresol 1.72 mg/ml (16 mM), mannitol 30 mg/ml (165 mM), dibasic sodium phosphate dihydrate 1.25 mg/ml (7 mM), sodium chloride 1.75 mg/ml (30 mM), zinc chloride and zinc acetate up to a total concentration of 32.7 µg Zn^{2+}/ml (3 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml using aseptic technique.

The blood glucose profile of the formulation after subcutaneous injection was tested in a cross over study in fasted pigs and compared with the profile after separate, simultaneous injections of Insulin Aspart (example 8) and Insulin Detemir (example 9) in the same doses.



Example 2

100 U insulin per ml containing 85% (U/U) insulin aspart and 15% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 85 U/ml (510 nmol/ml), Insulin detemir 15 U/ml (360 nmol/ml), phenol 1.80 mg/ml (19 mM), *m*-cresol 2.06 mg/ml (19 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 0.9 mg/ml (5 mM), sodium chloride 1.2 mg/ml (20 mM), zinc chloride and zinc acetate up to a total concentration of 28.4 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml using aseptic technique.

Example 3

100 U insulin per ml containing 70% (U/U) insulin aspart and 30% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 70 U/ml (420 nmol/ml), Insulin detemir 30 U/ml (720 nmol/ml), phenol 1.80 mg/ml (19 mM), *m*-cresol 2.06 mg/ml (19 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 0.9 mg/ml (5 mM), sodium chloride 1.2 mg/ml (20 mM), zinc chloride and zinc acetate up to a total concentration of 31.1 µg Zn^{2+}/ml (2.5 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.20. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml or 3 ml as well as vials 2 ml using aseptic technique.

Example 4

100 U insulin per ml containing 50% (U/U) insulin aspart and 50% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 50 U/ml (300 nmol/ml), Insulin detemir 50 U/ml (1200 nmol/ml), phenol 1.80 mg/ml (19 mM), *m*-cresol 2.06 mg/ml (19 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 0.9 mg/ml (5 mM), sodium chloride 1.2 mg/ml (20 mM), zinc chloride and zinc acetate up to a total concentration of 49 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide

were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml or 3 ml as well as vials 2 ml using aseptic technique.

Example 5

100 U insulin per ml containing 30% (U/U) insulin aspart and 70% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 30 U/ml (180 nmol/ml), Insulin detemir 70 U/ml (1680 nmol/ml), phenol 1.80 mg/ml (19 mM), *m*-cresol 2.06 mg/ml (19 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 0.9 mg/ml (5 mM), sodium chloride 1.2 mg/ml (20 mM), zinc chloride and zinc acetate up to a total concentration of 60.8 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.60. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml or 3 ml as well as vials 2 ml using aseptic technique.

Example 6

100 U insulin per ml containing 15% (U/U) insulin aspart and 85% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 15 U/ml (90 nmol/ml), Insulin detemir 85 U/ml (2040 nmol/ml), phenol 1.80 mg/ml (19 mM), *m*-cresol 2.06 mg/ml (19 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 0.9 mg/ml (5 mM), sodium chloride 1.2 mg/ml (20 mM), zinc chloride and zinc acetate up to a total concentration of 69.6 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml using aseptic technique.

Example 7

100 U insulin per ml containing 50% (U/U) insulin aspart and 50% (U/U) insulin detemir

A solution with the following composition was prepared: Insulin aspart 50 U/ml (300 nmol/ml), Insulin detemir 50 U/ml (1200 nmol/ml), phenol 1.80 mg/ml (19 mM), *m*-cresol 2.06

mg/ml (19 mM), mannitol 30 mg/ml (165 mM), dibasic sodium phosphate dihydrate 0.9 mg/ml (5 mM), sodium chloride 1.2 mg/ml (20 mM), zinc chloride and zinc acetate up to a total concentration of 49 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml or 3 ml as well as vials 2 ml using aseptic technique.

Example 8

Insulin aspart 600 nmol/ml (reference)

A solution with the following composition was prepared: Insulin aspart 100 U/ml (600 nmol/ml), phenol 1.50 mg/ml (16 mM), *m*-cresol 1.72 mg/ml (16 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 1.25 mg/ml (7 mM), sodium chloride 1.75 mg/ml (30 mM), zinc chloride up to a total concentration of 19.6 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml using aseptic technique.

Example 9

Insulin detemir 1200 nmol/ml (reference)

A solution with the following composition was prepared: Insulin detemir 50 U/ml (1200 nmol/ml), phenol 1.50 mg/ml (16 mM), *m*-cresol 1.72 mg/ml (16 mM), glycerol 16 mg/ml (174 mM), dibasic sodium phosphate dihydrate 1.25 mg/ml (7 mM), sodium chloride 1.75 mg/ml (30 mM), zinc chloride up to a total concentration of 39.2 µg Zn^{2+}/ml (3.0 Zn^{2+}/hexamer). Hydrochloric acid and sodium hydroxide were used for dissolution of the insulin and adjustment of pH to 7.40. Finally the solution was sterilized by filtration and filled into sterile Penfill® cartridges 1.5 ml using aseptic technique.

CLAIMS:

1. A pharmaceutical soluble formulation comprising insulin aspart and insulin detemir wherein the ratio between insulin aspart and insulin detemir is in the range from 15:85 to 85:15, on a unit to unit basis.

2. The formulation, according to claim 1 or 2, wherein the pH value is in the range from about 7 to about 8.

3. The formulation, according to any one of the preceding claims, further containing an agent rendering the solution isotonic, an antimicrobial preservative, a pH-buffering agent, and a suitable zinc salt.

4. The formulation, according to any one of the preceding claims, wherein the concentration of insulin is in the range from about 10 U/ml to about 1500 U/ml, preferably in the range from about 40 U/ml and about 1000 U/ml, even more preferred in the range from about 100 U/ml and about 500 U/ml.

5. The formulation, according to any one of the preceding claims, wherein the preservative is phenol, *m*-cresol or a mixture of phenol and *m*-cresol.

6. The formulation, according to any one of the preceding claims, wherein the total concentration of phenol and *m*-cresol is in the range from about 20 mM to about 50 mM, preferably in the range from about 30 mM to about 45 mM.

7. The formulation, according to any one of the preceding claims, containing zinc ions at the disposal of insulin in proportions in the range from about 2.3 to about 4.5 Zn^{2+} per insulin hexamer (corresponding to a range from about 0.38 to about 0.75 Zn^{2+} per insulin monomer).

8. The formulation, according to any one of the preceding claims, wherein the zinc salt is zinc chloride, zinc oxide, or zinc acetate.

9. The formulation, according to any one of the preceding claims, containing halogenide ions, preferably as sodium chloride, in an amount corresponding to from about 1 to about 100 mM, preferably from about 5 to about 40 mM.

10. The formulation, according to any one of the preceding claims, containing as isotonic agent glycerol, mannitol, sorbitol, or a mixture thereof in a concentration in the range from about 100 to about 250 mM.

11. The formulation, according to any one of the preceding claims, wherein the pH-buffer is sodium phosphate, TRIS (trometamol), N-glycylglycine, or L-arginine.

12. The formulation, according to any one of the preceding claims, wherein the pH-buffer is a physiologically acceptable buffer in a concentration in the range from about 3 mM to about 20 mM, preferably from about 5 mM to about 15 mM.

13. The use of insulin aspart in an amount in the range from about 15 % to about 85 %, of the total amount of insulin component calculated on a unit to unit basis to prepare a solution having both a fast-acting and a long-acting insulin component.

14. The use, according to any one of the two preceding claims, which is characterized by any of the features mentioned specifically in any of the above sub claims to pharmaceutical compositions.

15. A method of treating diabetes in a patient in need of such treatment, comprising administering to a patient a therapeutically effective amount of a pharmaceutical formulation according to any one of the preceding claims to formulations.

16. A method, according to the previous claims, which is characterized by any of the features mentioned specifically in any of the above sub claims to pharmaceutical compositions.

17. Any novel feature or combination of features described herein.

Novo Nordisk A/S

INTERNATIONAL SEARCH REPORT

PCT/DK 03/00239

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/28 C07K14/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, EMBASE, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 948 751 A (BALSCHMIDT PER ET AL) 7 September 1999 (1999-09-07) claims 1,9,14 ---	1-17
X	WO 00 43034 A (LI SHUN ;LILLY CO ELI (US); NG KINGMAN (US); WATTS ERIC ALAN (US)) 27 July 2000 (2000-07-27) claim 1	13
A	claims 1-59 --- -/--	1-12, 14-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2003	12. 08. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fernando Farieta

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAGUE PHILIPPE ET AL: "Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart." DIABETES CARE. UNITED STATES MAR 2003, vol. 26, no. 3, March 2003 (2003-03), pages 590-596, XP002249363 ISSN: 0149-5992 the whole document	13
A		1-12, 14-17
A	BRANGE J ET AL: "Monomeric insulins and their experimental and clinical implications." DIABETES CARE. UNITED STATES SEP 1990, vol. 13, no. 9, September 1990 (1990-09), pages 923-954, XP002249364 ISSN: 0149-5992 the whole document	1-17
A	SIMON R. HELLER: "Insulin Analogues" CURRENT MEDICAL, RESEARCH AND OPINION, vol. 18, no. 1, 2002, pages 40-47, XP002249365 the whole document	1-17
A	EP 0 383 472 A (LILLY CO ELI) 22 August 1990 (1990-08-22) claims 1-27	1-17
A	US 6 174 856 B1 (LANGBALLE PETER ET AL) 16 January 2001 (2001-01-16) claims 1-19	1-17

INTERNATIONAL SEARCH REPORT

PCT/DK 03/00239

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-16
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 13-14 and 17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 15-16

Claims 15-16 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claims.The search has been based on the alleged effects of the compounds or compositions.

Continuation of Box I.2

Claims Nos.: 13-14 and 17

Present claim 13 relates to an extremely large range for the use of insulin aspart, namely between 15% to 85%.Support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the formulations containing such range claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the examples 1-9 in the description.

According to Article 6 PCT the claim or claims shall define the matterfor which protection is sought and the claims shall be clear and concise. Simply referring to "any of the features" of previous claims or "any novel feature" described herein it is not considered clear and concise. Claims 14 and 17 have only been searched for subject matter covering by claims 1-12 and 15-16.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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